New Insights Into the Structure of Biological Membranes From Molecular Simulations

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Advances in availability of high-performance computers and improvements in the efficiency of molecular simulation software have made it possible to do meaningful simulations of heterogeneous membranes that include multiple species of phospholipid and the include sterols such as cholesterol in addition to phospholipid. The increased high performance computation available stems from the increased capacity of centralized supercomputing centers and from the ability to inexpensively build local clusters as powerful supercomputers were a few years ago. Major software improvements include the much faster scalar speed of the Gromacs molecular dynamics package than any other previous package, plus our application of Configuration Bias Monte Carlo to speed up the equilibration of membrane simulations by more efficient conformational sampling. Our simulations provide a "computational microscope", permitting us to look in quantitative detail at atomic scale bases for membrane organization.

Major results from our project in the last two years include:

1. We have replicated experimental results showing the creation of a condensed state by addition of 10% or more cholesterol to phosphatidylcholine membranes and uncovered the cholesterol-phosphatidylcholine hydrogen-binding patterns that define the tiling of the condensed phase of this system.
2. We have done the first monolayer and bilayer simulations of the same lipid under the same conditions in order to assess the differences and similarities between a bilayer and the corresponding monolayer at an air-water interface. For the sphingomyelin system we studied, we show that there is essentially exact correspondence between the monolayer and one leaflet of a bilayer except for the magnitude of undulations, which are significantly higher for the monolayer.
3. We have launched simulations of a sphingomyelin-cholesterol raft surrounded by fluid phosphatidylcholine. At this writing, this massive simulation is in progress, but there is already one qualitative observation to be made. The surface of the composite membrane system with the two-component raft in the fluid surround is much smoother than a system with any one or two of the three components. This suggests that the extra degree of packing freedom provided by the formation of gel/fluid adjacent domains at this scale relieves packing frustration and improves the stability of the bilayer.

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